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specific for said bacteriophage, allowing said mixture to sediment, wherein the step of sedimentation is effected by centrifugation, and observing the location of said portion of said cells, wherein strong agglutination of said portion of said cells is indicated by the cells being located upon or within a top layer of said inert particles and weak agglutination of said cells is indicated by the cells being located within a lower layer of said inert particles and no agglutination is indicated by the cells being located at the bottom of said microtube.

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18. The method of claim 10, wherein said antigen is a red blood cell antigen.

19. The method of claim 10, wherein said antigen is a HLA antigen.

REMARKS

Claims 10-23 are pending in the application. Claims 10-19 are under consideration. Claims 1-9 and 24-29 were canceled previously, without prejudice, by Preliminary Amendment filed September 29, 1999, and claims 20-23 have been withdrawn from further consideration as being drawn to a non-elected invention following election, without traverse, in the Response to the Restriction Requirement filed February 22, 2002 (Paper No. 8).

Claims 11, 18, and 19 have been amended herein. Support for these amendments is found throughout the specification as filed, as more fully set forth below. Thus, no new matter has been added by way of these amendments.

Objection to Claim 11 under 37 C.F.R. 1.75(c)

Claim 11 stands objected to as being of improper dependent form because it is the view of the Examiner that dependent claim 11 uses a sedimentation step "effected by centrifugation," while independent claim 10 indicates that sedimentation is carried our "under the force of gravity." It is the assertion of the Examiner that the force of gravity and centrifugal force are different forces of nature and, hence, dependent claim 11 fails to further limit independent claim 10. While not necessarily agreeing with the reasoning of the Examiner, in order to expedite prosecution of the application, Applicants have amended claim

11 by rewriting it in independent form to recite a sedimentation step "effected by centrifugation." This amendment introduces no new matter and is fully supported throughout the specification as filed (see page 5, line 23, page 6, line 1, page 22, lines 11-14, and 23-28, page 23, lines 3-6, and pages 25-45).

Rejection of Claims 10-19 Pursuant to 35 U.S.C. § 112, second paragraph

Claims 10-19 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully submit that the claims are not vague and indefinite, as more fully set forth below.

At page 3 of the Office Action, the Examiner contends that claim 10 is vague and indefinite in the recitation "inert particles and a second antibody," because it is the view of the Examiner that it is unclear whether the second antibody is attached to the inert particles or is simply an additional reagent in the microtube. Applicants respectfully traverse this rejection for the following reasons.

Applicants submit that the term "inert particles and a second antibody," as used, is a term of art which is well-known in the art of cellular and molecular biology, and a skilled artisan, based upon the specification as filed, would have understood that the invention encompasses the methods described in the specification as filed and is clearly exemplified therein.

It is settled law that the "patent law allows the inventor to be his own lexicographer." *Chicago Steel Foundry Co. v. Burnside Steel Foundry Co.*, 132 F.2d 812 (7th Cir. 1943). *See also* MPEP § 2173.01. This is because "[t]he dictionary does not always keep abreast of the inventor. It cannot. Things are not made for the sake of words, but words for things." *Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Further, applicant is entitled to have the claims construed in connection with the other parts of the application. *See Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Therefore, Applicants are entitled to define terms to describe their invention and the claims must be interpreted in light of the other parts of the application including the disclosure in the specification and the definitions provided therein. Applicants respectfully submit that when claim 10 is interpreted in light of the disclosure of the specification and the definitions set forth therein, it is clear that claim 10 and its dependent

claims are in no way indefinite since the specification clearly defines, exemplifies, and demonstrates the reduction to practice of various methods for detecting cell agglutination wherein inert particles and second antibodies are utilized. Applicants argue that the claim 10 as recited encompasses agglutination techniques in which the secondary antibody is not attached to inert particles, which techniques are described throughout the specification as filed (page 5, lines 16-23, page 7, lines 18-29, page 8, lines 1-12, page 22, line 3 to page 23 line 2, page 29, lines 9-16, page 34, lines 12-20 page 43, lines 2-19, Figures 1-6, and Table 2). Techniques such as cell "capture," in which the secondary antibody is attached to inert particles, are specifically described, and language such as "inert particles which have bound thereto a second antibody specific for said bacteriophage" is used for the cell capture technique disclosed in the specification (page 6, lines 12-23, page 8, lines 13-23, page 24, lines 10-15 and 20-28). Therefore, techniques in which a secondary antibody is or is not attached to inert particles are specifically delineated in the specification.

Therefore, Applicants submit that when claim 10 is interpreted in light of the disclosure of the specification and the definitions set forth therein, it is clear that claim 10 is in no way indefinite because the specification clearly defines, exemplifies, contemplates, and demonstrates the reduction to practice of methods for the use of inert particles and second antibodies for agglutination techniques.

The Examiner also asserts that claim 10 is vague and indefinite in the recitations of "located upon or within a top layer" and "located within a lower layer," because it is the opinion of the Examiner that it is unclear the distance required to distinguish a top layer from a lower layer. Applicants traverse this rejection and submit that the terms "located upon or within a top layer" and "located within a lower layer," as used, are terms of art which are well-known in the art of cellular and molecular biology, and a skilled artisan, based upon the specification as filed, would have understood that the invention encompasses the sedimentation methods described in the specification as filed and is clearly exemplified therein.

As more fully described above, Applicants are entitled to define terms to describe their invention, and the claims must be interpreted in light of the other parts of the application including the disclosure in the specification and the definitions provided therein.

Applicants respectfully submit that when claim 10 is interpreted based on the disclosure of the specification and the definitions and examples provided therein, as well as those techniques known to those of skill in the art not described therein, it is clear that claim 10 and its dependent claims are in no way indefinite because the specification clearly defines, exemplifies, and demonstrates the reduction to practice of various methods for detecting cell agglutination wherein differences in sedimentation position relative to the layer of inert particles is a measure of cell agglutination (see page 5, lines 23-28, page 6, lines 9-10, and 20-23, page 7, lines 24-29, especially page 22, line 10 to page 23, line 11 and page 29, lines 9-16, pages 43-44, and Figures 1-6). Therefore, an artisan skilled in the techniques of cell agglutination and cell separation would understand that agglutinated cells can be separated based on localization from the top layer in a microtube relative to the bottom of the tube. Applicants assert that claim 10 merely recites a method routinely used by those skilled in the art.

In addition, the specification provides, at page 16, lines 6-9, that prior to agglutination or capturing, cells may be rendered "visible" by staining or other labeling techniques in order that agglutination or capturing is apparent to the naked eye or scanner. Thus, the specification discloses multiple methods for detecting agglutinated cells which can be used in the method recited in claim 10.

Therefore, Applicants submit that when claim 10 is interpreted in light of the disclosure of the specification and the definitions set forth therein, it is clear that claim 10 is in no way indefinite because the specification clearly defines, exemplifies, contemplates, and demonstrates the reduction to practice of methods for detecting cell agglutination. The method comprises, inter alia, adding a mixture containing inert particles and a second antibody, in which agglutinated cells can be detected based on their sedimentation in a microtube relative to non-agglutinated cells.

Claims 18 and 19 stand rejected as being vague and indefinite because it is the view of the Examiner that the recitation of "antigen-bearing moiety" lacks antecedent basis in claim 10. Although not necessarily agreeing with the reasoning of the Examiner, Applicants, in a good faith effort to expedite prosecution of the application, have amended claims 18 and 19 to recite "antigen." These amendments recite no new subject matter and are fully

supported by the specification and claims as filed (page 9, lines 6-14, page 15, line 27 to page 16, line 2, and pages 25-45). Therefore, Applicants respectfully submit that the rejection of claims 18 and 19 has been rendered moot by the amendments set forth herein and that this rejection should be reconsidered and withdrawn in view of these amendments.

Applicants respectfully submit that claims 10-19, including claims 11, 18 and 19 as amended, are not indefinite under 35 U.S.C. § 112, second paragraph, nor are their dependent claims. Thus, Applicants request that the rejection of claims 10-19 be reconsidered and withdrawn.

Rejection of Claims 10-19 Pursuant to 35 U.S.C. § 112, first paragraph

Claims 10-19 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. It is the opinion of the Examiner that the claimed method utilizes "inert particles and a second antibody." However, it is the view of the Examiner that there is no indication whether the second antibody is attached to the inert particles in the manner of an indirect agglutination immunoassay or whether the antibodies are separate reagents intended to agglutinate the bacteriophage-cell complexes themselves while the inert particles serve a different function in the assay.

Applicants respectfully traverse the rejection of claims 10-19 under 35 U.S.C. § 112, first paragraph, for the reasons set forth below.

It is well-settled that an applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*,

537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled in the art and is already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed, so long as it is not undue.

Under the present patent law, claims 10-19 are amply enabled by the specification as filed under 35 U.S.C. § 112, first paragraph. More specifically, claims 10-19 recite methods useful for detecting cell agglutination, comprising: adding a mixture of cells and a population of bacteriophage expressing a first antibody, said first antibody being specific for an antigen expressed by at least a portion of the cells, wherein the first antibody binds to the cells causing the bacteriophage to also bind to the cells, then adding the mixture to a microtube containing inert particles and a second antibody specific for the bacteriophage, allowing the mixture to sediment, measuring the amount of agglutination based on the relative position of the cells in the microtube, and the use of various cells, bacteriophage, antibodies, and antigens (see pages 10-45). The specification as filed amply supports these claims because the skilled artisan, armed with the methods, bacteriophage, cells, antigens, and antibodies disclosed in the specification, would have been able to identify, through routine experimentation, methods of detecting agglutination having the disclosed characteristics as recited by the claims, and to practice the invention commensurate with the scope of the claims without undue experimentation.

Further, one of skill in the art would also be able to identify a variety of methods of detecting cell agglutination, following the teachings, methods, bacteriophage, cells, antibodies, and antigens, set forth in the specification as filed and/or as known in the art, based upon the disclosure provided in the specification without undue experimentation. That is, the crucial novel teachings of the invention, *inter alia*, the use of agglutination techniques comprising a second antibody and inert particles (page 5, lines 16-23, page 7, lines 18-29, page 8, lines 1-12, page 22, line 3 to page 23 line 2, page 29, lines 9-16, page 34, lines 12-20 page 43, lines 2-19, Figures 1-6, and Table 2), utilizing differences in sedimentation position

relative to the layer of inert particles as a measure of cell agglutination (see page 5, lines 23-28, page 6, lines 9-10, and 20-23, page 7, lines 24-29, especially page 22, line 10 to page 23, line 11 and page 29, lines 9-16, pages 43-44, and Figures 1-6), methods to rendered cells "visible" by staining or other labeling techniques in order that agglutination is apparent to the naked eye or scanner (page 16, lines 6-9), are amply disclosed in the specification as filed. For example, the specification as filed discloses various methods to detect cell agglutination (see Figures 1-6, Tables 1 and 2, and Examples at pages 15-45), including various cells, bacteriophage, antibodies and antigens which are useful in the present invention.

Therefore, the application merely omits that which is well-known to those skilled in the art and is already available to the public, i.e., other agglutination assays and/or modifications of the agglutination assays described herein. Moreover, methods and assays for detecting cell agglutination are disclosed in the specification as filed, and/or such methods are known to those skilled in the art and the practice of such methods is routine in the art and should not be considered an undue burden (see, for example, page 22, line 10 to page 23, line 11; Figures 1-6, Tables 1-2, and Examples), since they were routinely performed by one skilled in the art. Thus, while the experimentation may be complex, it is certainly not undue where, as here, the art typically engaged in such experimentation at the time the specification was filed, and where there had been extensive reduction to practice where none is required. Further, as described above, the specification and claims as filed clearly distinguish between detecting cell agglutination using a second antibody and inert particles, and a cell capture assay using a second antibody attached to inert particles.

Applicants have disclosed sufficient data to support claims reciting methods for detecting cell agglutination comprising adding a mixture of cells and a population of bacteriophage expressing a first antibody, said first antibody being specific for an antigen expressed by at least a portion of the cells, wherein the first antibody binds to the cells causing the bacteriophage to also bind to the cells, then adding the mixture to a microtube containing inert particles and a second antibody specific for the bacteriophage, allowing the mixture to sediment, measuring the amount of agglutination based on the relative position of the cells in the microtube, and the use of various cells, bacteriophage, antibodies, and antigens (see pages 10-45, Figures 1-6, and Tables 1 and 2). The specification as filed also discloses

multiple assays and techniques for various agglutination assays, the cells to be assayed, and the bacteriophage, antigens and antibodies to be used. Thus, the skilled artisan would be able, without undue experimentation, to determine whether a method to detect cell agglutination would possess the requisite characteristics.

Further, it is clear that the level of skill in the art would allow an artisan to easily test various cell agglutination detection assays based on the disclosure in the specification as filed, and having the desired properties as defined, exemplified, and disclosed by the Applicants. One skilled in the art of screening cell agglutination assays for those possessing a desired biological activity or characteristic typically engaged in this type of experimentation at the time the specification was filed (see pages 10-45). This is important because the present case law regarding enablement under 35 U.S.C. § 112, first paragraph, allows significant experimentation without finding it undue if the art typically engages in such experimentation.

In the landmark enablement case of *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as here, the art typically screens numerous assays, cells, antibodies, and antigens for the desired characteristic, e.g., capable of detecting cell agglutination, where various components and their uses and markers for measuring the activity of the assay are disclosed in the specification as filed, where the specification discloses specific components and specific markers, demonstrating extensive reduction to practice, one skilled in the art would not require undue experimentation to identify a method of detecting cell agglutination having the desired characteristics.

Thus, where one skilled in the art routinely screens antibodies, cells and methods for detecting cell agglutination, where methods have been reduced to practice, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely

> finding another analogous catalyst complex which could be used in "forming hydroperoxides."
>
> *In re Angstadt*, 190 USPQ at 218 (citations omitted).

Thus, where methods for assessing whether a claimed method of detecting cell agglutination having the utility of the claimed methods and is well-known in the art and/or disclosed in the specification, and where working examples are disclosed (see Figures 1-6, Tables 1 and 2, and Examples), it would not be undue experimentation to screen and identify methods and components which have the disclosed utility where the art typically engages in such experimentation.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely assays methods of detecting cell agglutination and the components used therein for the asserted utility (*e.g.*, detecting cell agglutination), it is not undue experimentation for them to do so.

In sum, Applicants respectfully submit that the claims are amply supported by the disclosure provided in the specification as filed, and that numerous working examples, which are not even required under the present law regarding enablement, are provided. Therefore, undue experimentation would not be required of a skilled artisan to make and/or

use the full scope of the invention as recited in claims 10-19. Given the advanced state of the relevant art, the ample disclosure, and the extensive reduction to practice provided in the specification as filed, claims 10-19 are amply enabled and this requirement of 35 U.S.C. § 112, first paragraph, has been satisfied. Thus, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each objection and rejection of the Examiner to the present application has been either overcome or is now inapplicable, and that each of claims 10-19 is now in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,
DONALD L. SIEGEL *ET AL.*

August 6, 2002
(Date)

By: _____

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Enclosures ("Marked-up" copy of the claims)

MARKED UP COPY OF AMENDED CLAIMS

Please amend claims 11, 18, and 19 as set forth below.

11. [The method of claim 10,] A method of detecting cell agglutination, comprising providing a mixture comprising a population of cells and a population of bacteriophage expressing a first antibody on the surface of said bacteriophage, said first antibody being specific for an antigen expressed by at least a portion of the cells in said cell population, wherein said first antibody binds to said portion of said cells causing said bacteriophage to also bind to said portion of said cells, adding said mixture to a microtube containing inert particles and a second antibody specific for said bacteriophage, allowing said mixture to sediment, wherein the step of sedimentation is effected by centrifugation, and observing the location of said portion of said cells, wherein strong agglutination of said portion of said cells is indicated by the cells being located upon or within a top layer of said inert particles and weak agglutination of said cells is indicated by the cells being located within a lower layer of said inert particles and no agglutination is indicated by the cells being located at the bottom of said microtube.

18. The method of claim 10, wherein said antigen[-bearing moiety] is a red blood cell antigen.

19. The method of claim 10, wherein said antigen[-bearing moiety] is a HLA antigen.